

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

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China 10th Floor, Building 1 10 Caihefang Road,
Haidian District, Beijing

LIU, SHEN & ASSOCIATES

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Applicant's or agent's file reference F20W6702		Date of mailing (day/month/year) 29 July 2020
International application No. PCT/CN2020/088585		FOR FURTHER ACTION See paragraph 2 below
International filing date (day/month/year) 05 May 2020	Priority date (day/month/year) 05 May 2019	
International Patent Classification (IPC) or both national classification and IPC C07D 471/04(2006.01)i; C07D 401/14(2006.01)i; A61K 31/506(2006.01)i; A61P 35/00(2006.01)i		
Applicant QILU REGOR THERAPEUTICS INC.		

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☒ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/ National Intellectual Property Administration, PRC China 6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088	Date of completion of this opinion 23 July 2020	Authorized officer LIU,Guangyu
Facsimile No. (86—10) 62019451		Telephone No. 86-(010)-53962142

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Box No. I

Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a)).
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 25-33

because:

☒ the said international application, or the said claims Nos. 25-33 relate to the following subject matter which does not require an international search (*specify*):

[1] Claims 25-33 are directed to the methods for the treatment of human or animal body by therapy. But the opinion has been carried out and based on the following subject matter: the use of a compound according to any one of claims in the manufacture of medicaments for the treatment of diseases.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13*ter*.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement																		
1. Statement	<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 35%; vertical-align: top;">Novelty (N)</td> <td style="width: 35%; border-bottom: 1px solid black;">Claims 1-33</td> <td style="width: 30%; text-align: right; vertical-align: bottom;">YES</td> </tr> <tr> <td></td> <td style="border-bottom: 1px solid black;">Claims None</td> <td style="text-align: right; vertical-align: bottom;">NO</td> </tr> <tr> <td style="vertical-align: top;">Inventive step (IS)</td> <td style="border-bottom: 1px solid black;">Claims None</td> <td style="text-align: right; vertical-align: bottom;">YES</td> </tr> <tr> <td></td> <td style="border-bottom: 1px solid black;">Claims 1-33</td> <td style="text-align: right; vertical-align: bottom;">NO</td> </tr> <tr> <td style="vertical-align: top;">Industrial applicability (IA)</td> <td style="border-bottom: 1px solid black;">Claims 1-33</td> <td style="text-align: right; vertical-align: bottom;">YES</td> </tr> <tr> <td></td> <td style="border-bottom: 1px solid black;">Claims None</td> <td style="text-align: right; vertical-align: bottom;">NO</td> </tr> </table>	Novelty (N)	Claims 1-33	YES		Claims None	NO	Inventive step (IS)	Claims None	YES		Claims 1-33	NO	Industrial applicability (IA)	Claims 1-33	YES		Claims None	NO
Novelty (N)	Claims 1-33	YES																	
	Claims None	NO																	
Inventive step (IS)	Claims None	YES																	
	Claims 1-33	NO																	
Industrial applicability (IA)	Claims 1-33	YES																	
	Claims None	NO																	
2. Citations and explanations :	[1] I. Cited documents [2] D1: WO 2010075074A1 [3] D2: WO 2016014904A1 [4] D3: WO 2016141881A1 [5] II. Novelty [6] D1 discloses a compound of formula (I) or a pharmaceutically acceptable salt thereof which is useful in the treatment of cell proliferative diseases (abstract, claims 1, 18-20). D1 also discloses specific compounds (description, examples 1-14). The compounds in D1 are CD4/6 inhibitors (description, page 1, line 30 to page 2, line 2). D1 further discloses the pharmaceutical composition (claim 17). [7] D2 discloses compounds of formula (I) or pharmaceutically acceptable salts thereof as cyclin-dependent kinase (CDK) and cell proliferation inhibitors which are useful for treating diseases and disorders associated with activity of CDK, in particular CDK4/6, including but not limited to various cancers and inflammation diseases or conditions (abstract, claims 1, 15-27). D2 also discloses specific compounds (description, examples 1-31). D2 further discloses the pharmaceutical composition (claim 14). [8] D3 discloses a compound of formula (I) or a pharmaceutically acceptable salt thereof serving as a selective CDK4/6 inhibitory activity (abstract, claim 1). The compounds in D3 can be used to treat tumor (description, page 2, paragraph 2). D3 also discloses specific compounds (claim 12). D3 further discloses the pharmaceutical composition (description, page 9, paragraphs 3-6). [9] Claims 1-33 are not disclosed by D1-D3 and they are novel in the sense of PCT Article 33(2). [10] III. Inventive step [11] The difference between the subject matter of claim 1 and any one of the specific compounds in D1-D3 is that ring A in claim 1 is different from the corresponding part in D1-D3. The problem to be solved by the present invention may therefore be regarded as providing an alternative CDK inhibitor. [12] However, =CH- and =N- are bioisosteres, and -CH₂-, -O-, -S- and -NH- are bioisosteres. It is conventional technical skills for the person skilled in the art to alter the substitute positions of the substitute groups. The person skilled in the art would be motivated to modify any one of the specific compounds in D1-D3 with bioisosteres and alter the substitute positions of the substitute groups. Therefore, it would be obvious for the person skilled in the art to arrive at the subject matter of claim 1, and claim 1 does not involve an inventive step in the sense of PCT Article 33(3). [13] D1-D3 disclose the pharmaceutical compositions and the methods of inhibiting CDK and treating tumor. Since the compound of any one of claims 1-23 or a pharmaceutically acceptable salt, or a stereoisomer thereof does not involve an inventive step, claims 24-26 do not involve an inventive step in the sense of PCT Article 33(3). [14] Dependent claims 2-23, 27-33 do not disclose any special technical features which the person skilled in the art would regard as more than a normal design option. The person skilled in the art would obviously apply these features in order to solve the problem posed. Therefore, they do not involve an inventive step in the sense of PCT Article 33(3).																		

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Box No. V

**Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability;
citations and explanations supporting such statement**

[15] IV. Industrial Applicability

[16] Claims 1-33 can be used in drug industry. Therefore, claims 1-33 are industrially applicable in the sense of PCT Article 33(4).

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Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

- [1] Claims 4-22, 33 are multiple dependent claims, but they refer to the preceding multiple dependent claims. Therefore, claims 4-22, 33 do not meet the criteria set out in PCT Rule 6.4(a).

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

- [1] The term of "e.g." in claims 29, 32 and the term of "such as" in claims 32-33 define different scopes. Therefore, claims 29, 32-33 are not clear and do not meet the criteria set out in PCT Article 6.
- [2] However, the opinion is based on the assumption that all of the scopes are considered.